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APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 31, 2017
From	Theresa M. Michele, MD Director, Division of Nonprescription Drug Products
Subject	Division Director Summary Review
NDA/BLA #	209089 (tablet), 209090 (oral solution)
Applicant Name	Union Chimique Belge, Inc. (UCB) Agent: Sanofi US Services Inc.
Date of Submission	March 31, 2016
PDUFA Goal Date	January 31, 2017
Proprietary Name / Established (USAN) Name	Xyzal Allergy 24HR (levocetirizine dihydrochloride) Children's Xyzal Allergy 24HR (levocetirizine dihydrochloride)
Dosage Forms / Route of Administration / Strength	Allergic rhinitis (seasonal and perennial): • Tablet, 5 mg (adults and children 6-64 years of age) • Oral solution 2.5 mg/5 mL (adults and children ages 2-64 years)
Proposed Indication(s)	Temporary relieves these symptoms due to hay fever or other respiratory allergies: runny nose; sneezing; itchy, watery eyes; itching of the nose or throat
Recommended Regulatory Action	Approval

1 INTRODUCTION

On behalf of UCB, Inc., Sanofi US Services, Inc. (Sanofi) submitted these 505(b)(2) new drug applications seeking approval for levocetirizine dihydrochloride tablets and oral solution (levocetirizine; proposed trade names Xyzal Allergy 24HR and Children's Xyzal Allergy 24HR), (b) (4) for OTC use for the temporary relief of symptoms due to hay fever or other respiratory allergies, including runny nose; sneezing; itchy, watery eyes; and itching of the nose or throat.

Levocetirizine is a histamine H_1-receptor antagonist, which is the R-enantiomer of the racemate, cetirizine. As such, the sponsor references not only the levocetirizine prescription NDAs 22064 (oral tablet) and NDA 22157 (oral solution), but also NDAs 19835, 21621, and 20346 for the Zyrtec (cetirizine dihydrochloride) tablets, chewable tablets, and oral solution, respectively. Levocetirizine is approved as a prescription product for the management of symptoms of seasonal allergic rhinitis (SAR; adults and children ages 2 years and older), perennial allergic rhinitis (PAR; adults and children ages 6 months and older) and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU; adults and children ages 6 months and older). Dosing is 5 mg once daily in

the evening for adults and children ages 12 years and older, 2.5 mg once daily in the evening for adults and children ages 6 to 11 years, and 1.25 mg once daily in the evening for children ages 6 months to 5 years. There are dose adjustments required for various degrees of renal impairment ranging from 2.5 mg once daily for adults with mild renal impairment to a contraindication in patients with end-stage renal disease. The sponsor is proposing a partial switch of the SAR and PAR indications down to age 2 years. The indication for CIU and PAR indication for children younger than 2 years would remain prescription.

The indication that the sponsor is proposing "temporarily relieves these symptoms due to hay fever or other respiratory allergies: runny nose; sneezing; itchy, watery eyes; itching of the nose or throat" is consistent with other OTC products available for treatment of allergic rhinitis. However, Sanofi proposes that dosing of the product could occur (b) (4) (b) (4) in the evening to avoid somnolence as with the prescription product. To justify this dosing revision, Sanofi submitted analyses of clinical safety data from morning-dosed studies compared to evening-dosed studies.

The allergic rhinitis indications of SAR and PAR are considered to be similar for both prescription and OTC use, and consumer ability to understand and use products in this category is well established. As such, no new nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, clinical pharmacology, clinical efficacy or safety studies were submitted as part of this application. As part of this application, Sanofi conducted a label comprehension study in order to support warning language for kidney disease and urinary retention.

This summary review provides an overview of the application with a focus on the new dosing instructions and labeling.

2 BACKGROUND

2.1 Allergic rhinitis (seasonal and perennial)

Allergic rhinitis is a common IgE-mediated inflammatory condition characterized by one or more of the following symptoms: congestion, rhinorrhea (anterior and posterior), sneezing, and itching. Symptoms may significantly affect quality of life, and may be associated with sleep disturbance, fatigue, headache, cognitive impairment. Traditionally, allergic rhinitis is divided into two subsets, SAR and PAR, depending on the aeroallergens involved and persistence of symptoms. Although estimates vary, allergic rhinitis may affect as many as 30-60 million people in the US, including 10-30% of adults and up to 40% of children.[1]

Allergic rhinitis is a well-established OTC indication, with both monograph and NDA OTC products available in a variety of intranasal and oral formulations. These include first and second generation oral antihistamines, oral antihistamine/decongestant combination products, intranasal decongestants, and intranasal cromolyn. In addition, in October 2013, FDA approved the first intranasal corticosteroid as a prescription to OTC switch [Nasacort Allergy 24 HR (triamcinolone acetonide) nasal spray; NDA 20,468], with several

[1] The diagnosis and management of rhinitis: An updated practice parameter, Joint Task Force on Practice Parameters for Allergy and Immunology. 2008

subsequent OTC approvals of other nasal steroid products. Professional guidelines for the treatment of adults with allergic rhinitis recommend nasal steroids as first line therapy for moderate-severe disease with or without a second generation antihistamine.

The standard OTC indication language for allergic rhinitis, covering the prescription indications for both SAR and PAR, is derived from the OTC monograph indication for first generation antihistamines "temporarily relieves runny nose and sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies.[2]" While consumers can generally recognize the symptoms of allergic rhinitis, diagnosis of PAR in infants and children under the age of 2 years is more complex and requires the evaluation of a physician.

2.3 Relevant Regulatory History for fluticasone propionate

As part of this application, one formal pre-submission meeting was held between Sanofi/UCB and FDA regarding the content and format of the planned NDAs for the prescription to OTC switch of levocetirizine.

3 CHEMISTRY, MANUFACTURING, AND CONTROLS

Levocetirizine 5 mg tablets are white to off-white film-coated, oval, scored tablets. They may be split in half to give a 2.5 mg dose for children ages 6 to 11 who are able to swallow tablets. The liquid formulation is a clear, colorless solution at a concentration of 0.5 mg/mL (2.5 mg/5 mL) which is bioequivalent to the tablet. The sponsor states that there are no changes to the prescription quality information except for inclusion of a debossed tablet, new packaging configurations, (b) (4) the blister packages, and addition of new packaging sites. There is a shelf life of 36 months under room temperature storage conditions. To be in compliance with the USP salt policy of the active moiety, the established name should contain the active moiety in the neutral form without the name of the salt. However, to avoid confusion with the prescription product, which will remain on the market for the CIU indication, the quality team recommends accepting the proposed established name of "levocetirizine dihydrochloride". I concur with this recommendation as well as their recommendation for approval from a quality standpoint.

4 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

No new nonclinical data were submitted as part of this application. As the OTC product is the same as the prescription product, there are no new excipients or impurities. There are no outstanding nonclinical pharmacology/toxicology issues.

5 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

No new clinical pharmacology data were submitted as part of this application. According to the prescription label, levocetirizine is rapidly and extensively absorbed following oral administration and has a peak plasma concentration 0.9 hour after administration of the oral tablet without a food effect. The drug is excreted primarily through the kidney by both

[2] 21 CFR 341.72 Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Labeling of antihistamine drug products (1992, as amended Dec 6, 2002).

glomerular filtration and active tubular secretion, leading to a plasma half-life of approximately 8 to 9 hours after administration of either the tablet or oral solution. Excretion varies with renal function and the plasma blood levels increase approximately 6 fold in persons with end-stage renal disease. Because the adverse effect of somnolence is known to increase with increasing dose, dosing in the prescription setting is based on renal function. Levocetirizine is contraindicated in persons with end-stage renal disease or who are on hemodialysis. For the OTC label, the sponsor recommends the following warning: "Do not use if you have kidney disease." While an argument could potentially be made for a lesser warning of "ask a doctor before use if you have kidney disease," the sponsor has taken a conservative approach, which is reasonable. Furthermore, this warning was tested in a label comprehension study, with reasonably good comprehension.

There are no outstanding clinical pharmacology issues.

6 CLINICAL MICROBIOLOGY

Not applicable.

7 CLINICAL AND STATISTICAL EFFICACY

A large number of clinical trials have been conducted with levocetirizine, including a number of trials supporting the SAR and PAR, as well as pediatric dosing. The efficacy of levocetirizine for SAR and PAR has been previously established for the prescription product, so efficacy will be reviewed only briefly here, as the OTC indication is similar.

The clinical program for the prescription NDAs included a total of 12 clinical trials in allergic rhinits: 6 efficacy and safety trials in adult and adolescents with SAR or PAR (3 dose ranging, one pivotal trial in PAR, one pivotal trial in SAR, and one shorter duration trial), 2 efficacy and safety trials in children 6 to 12 years of age with SAR or PAR, 2 environmental exposure unit trials, and 2 long term safety trials. Efficacy in children under age 6 was extrapolated based on pharmacokinetic data.

Reflective total symptom scores (rTSS), a composite symptom score of rhinorrhea, sneezing, and nasal itching, and ocular itching) were evaluated over treatment periods of 2 to 4 weeks for SAR and PAR, respectively. Subjects treated with fluticasone propionate aqueous nasal spray (FPANS) exhibited significantly greater decreases in rTSS than placebo-treated patients (see product prescription labeling). In environmental chamber studies evaluating onset of action, a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 1 hour after treatment.

8 SAFETY

The safety profile of levocetirizine is well-characterized, including a large clinical trial database (primarily in SAR and PAR) of more than 6000 subjects exposed to levocetirizine, and postmarketing data from prescription approval in over 60 countries worldwide and in 12 countries as a nonprescription drug. The U.S. prescription label contains warnings and precautions related to sedation, avoiding concurrent use of alcohol or other CNS suppressants, and instructions to use with caution in patients with predisposing factors for urinary retention. As noted previously, dose adjustment for renal impairment (including

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